REMARKS

Claims 1 and 6-20 are pending in the instant application. Claims 1 and 6-20 have been rejected. Claims 1, 6-12, 14-18 and 20 have been canceled. Claims 13 and 19 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 102(b)

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Carroll et al. has been maintained for reasons of record. Claim 1 has been canceled. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1 and 6-12 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Carroll et al., in view of Bonner et al. (1986), Cook et al., and Skorski et al. The Examiner suggests that it would have obvious to one of ordinary skill in the art to make oligonucleotides directed to SEQ ID NO: 64 since the sequence was taught by Bonner et al., and since Carroll et

al. expressly teach antisense inhibition of c-raf, while the claimed modifications would have been obvious over the teaching of Cook et al., and the use of a chemotherapeutic agent is made obvious by the teaching of Skorski et al.

Applicant has canceled claims 1 and 6-12 making this rejection moot. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 12-20 have been rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. The Examiner acknowledges that the specification is enabling for antisense oligonucleotides of ISIS 5136 targeted to c-raf and used in the treatment of pancreatic, renal cell, colon or bladder cancer but suggests that the specification fails to enable any and all forms of cancer or ocular angiogensis, as well as any antisense compound. The Examiner cites articles he claims support the unpredictability of antisense. Applicant respectfully traverses this rejection.

At the outset, Applicant has amended the claims to recite they are directed to use of a specific oligonucleotide of SEQ ID NO: 8 for the treatment of the conditions acknowledged by the Examiner to be enabled by the specification as filed (i.e., pancreatic cancer, renal cell cancer, colon cancer, and bladder cancer). Applicant respectfully points out that this oligonucleotide corresponds to ISIS 5132, not 5136, but is the oligonucleotide shown throughout the specification to have activity *in vivo* to treat cancer.

Applicant disagrees with the Examiner's suggestion that the cited references support the position that application of antisense *in vivo* is highly unpredictable or problematic.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable and that predicting efficacy based on *in vitro* data is problematic. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also

occur in humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals, and then to testing in humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans. Further, the fact that *in vivo* data were provided for an exemplary antisense oligonucleotide, ISIS 5132 (SEQ ID NO: 8), should provide further proof that the compounds of the instant invention are not highly unpredictable

The paper by Braasch and Corey (2002) describes the advances that have been made in the design of antisense compounds over the years. Included in the discussion are the types of advances that are taught in the specification as filed. In fact, the paper states in the abstract that success in clinical trials with these agents has occurred. The Examiner, however, attempts to use this reference to emphasize that many obstacles persist in the art. This is not a proper use of this reference under 35 U.S.C. 112, first paragraph, as the teachings of a reference must be read in their entirety, not only in bits and pieces to support the

Examiner's interpretation. See MPEP 2141.02. A prior art reference must be considered in its entirety, *i.e.* as a whole, including portions that would lead away from the claimed invention. *W. L. Gore & Assocs., Inc. v. Garlock., Inc.*, 721 F. 2d 1540, 220 USPQ 303(Fed. Cir. 1983, *cert. denied*, 469 U.S. 851 (1984). This reference cites past problems and describes the advances that have been made in the design of antisense compounds over the years, including the types of advances that are taught in the specification as filed, so that antisense provides new potential both for research and clinical application. The authors conclude that:

> *Oligomers with improved chemical properties, combined with advances in cell biology and success in clinical trials, are affording powerful new options for basic research, biotechnology and medicine (p. 4503, Abstract).*

Nothing in the Braasch reference teaches that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment; in fact at page 4504, Braasch teaches (referring to references 8 and 14-16) that those skilled in the art know how to deliver antisense oligonucleotides into various organs of both humans and animals (see, Braasch at 4504, column

2, *Uptake by Cultured Cells and Tissue Distribution in Animals*). Braasch teaches that use of transfection agents is routine in most types of cultured cells, but in contrast, uncomplexed phosphorothioate oligonucleotides spontaneously enter a number of tissues, including liver, kidney, spleen, intestine and other organs, when introduced intravenously (citing reference 8), and that *(p)romising data from ongoing clinical studies also suggest that oligomers can enter human tumors upon intravenous administration and produce a therapeutic effect* (references 8, 14-16).

As for teachings regarding toxicity and immunological problems, the Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States. (MPEP 2107.01) These possible side effects are not relevant to patentability. Nor are artifacts that may have obscured the intended antisense mechanism in certain situations, for which the Examiner cites Braasch. Braasch cites reference 3 (Stein) on this point; Stein teaches ways known in the art for avoiding

nonspecific results, such as the importance of controls such as are taught in the instant specification.

Thus nothing in Braasch teaches or suggests that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment, nor does it teach that antisense compounds are inherently unpredictable when it comes to predicting *in vivo* activity based on well-designed *in vitro* studies.

Branch (1998) is also cited by the Examiner in support of his position. This paper teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. The Examiner, however, attempts to use this paper to support suggestions concerning the inaccessibility of most potential target RNA binding sites to antisense molecules and the unpredictability of antisense effects. One of skill in the art would not expect to predict the "winning" antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one best suited to his or her needs. Time and difficulty of experiments are not determinative

of enablement if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.(MPEP 2164.06). The fact that effective antisense drugs are selected from large pools of candidates and then optimized, rather than predicted *a priori*, does not indicate lack of enablement, *i.e.*, the need for undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Furthermore, the need to select an antisense compound from a pool of candidates is not unique to antisense drugs; all drugs are selected from large pools of candidates. While Braasch teaches that the limited number of freely accessible RNA regions means that it may be necessary to screen 20 or more oligomers before finding one that functions adequately, in fact this 1-in-20 likelihood of

success is high when compared to the odds of finding a traditional small molecule drug. Only five in 5,000 compounds make it from early research and preclinical testing to clinical trials, and of those five that enter clinical trials only one is approved (data from PhRMA, Pharmaceutical Research and Manufacturers of America).

The Office Action also cites Branch as supporting the unpredictability of non-antisense effects. The predictability, or lack thereof, of an effect which is not the claimed invention is irrelevant. One of ordinary skill is well aware of how to use proper controls to elucidate antisense inhibition of a desired target. Branch is also cited as teaching the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available (Page 46, second column). However, as discussed *supra*, the teachings of a reference must be read in its entirety, not only in bits and pieces to support the Examiner's interpretation. See MPEP 2141.02. The full excerpt which has been cited in part by the Examiner begins, "As is true of all pharmaceuticals, the value of a potential antisense drug"... In other words, antisense drugs are no different from any other drugs. If the need for

evaluation of dose-response and therapeutic index were a bar to patentability, no drug would be patentable. Clearly this is not the proper standard. Thus nowhere does the reference of Branch teach that one of skill would be unable to use the compounds or methods of the invention in an *in vivo* environment.

The paper by Tamm et al. (2001) is another more recent review of the antisense technology and its specific application to oncology. Again, although the use of antisense is discussed in terms of what can go wrong, the paper, again, describes advances such as those taught in the instant specification. Nowhere do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans. However, the Examiner cites this paper by Tamm concerning the undesirability of immunostimulation as a side effect and the unpredictability of this side effect, which, as discussed above, is irrelevant to the patentability of the claimed invention. Furthermore, Tamm teaches that the immunostimulatory activity can be ascertained experimentally, and can be avoided by several means.

As discussed for each of these references cited by the Examiner, the teachings of a reference must be read in its

entirety, not only in bits and pieces to support the Examiner's interpretation. See MPEP 2141.02. Tamm, in fact, when taken as a whole, has a positive tone regarding the feasibility of the antisense approach in the clinic. "The specificity of this mechanism has resulted in a new class of drugs with a wide range of potential clinical applications. One approved antisense drug, and results of several clinical antisense drug trials, show the feasibility of this approach, with some evidence for clinical efficiency." (Tamm, p. 489, column 2).

Two of the other references cited by the Examiner, Gewirtz et al. (1996) and Agrawal (1996), likewise provide no basis to conclude that extrapolation from *in vitro* data to effects in humans is unpredictable or especially problematic.

The Examiner suggests that Gewirtz teaches that the inhibitory activity of an oligonucleotide depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. Again, one of skill in the art would not need to predict an active antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one with inhibitory activity best suited to his or her needs. Such screening is taught in the

instant specification and is routine for those in the art. Thus there is no need to predict the activity of an antisense compound when, as for other types of drugs, it can routinely be determined without undue experimentation. Nowhere does Gewirtz teach that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment.

The Examiner suggests that the paper by Agrawal teaches difficulties in uptake of oligonucleotides by cells, and in particular that it is "difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (page 378) and that microinjection or lipid carriers may not be relevant for *in vivo* situations (page 379). As is well known in the art, there are many factors (discussed in Agrawal and elsewhere) that determine antisense efficacy and cellular uptake. There is, however, no requirement that all oligonucleotides (or all drugs of any class) behave identically.

As for the relevance of lipid carriers or microinjection for *in vivo* situations, the fact that these methodologies are irrelevant is not the same as a teaching that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment. In fact, as taught by Braasch and

discussed above, uncomplexed (*i.e.*, without lipid carriers) oligonucleotides have been demonstrated to enter a number of tissues, including liver, kidney, spleen, intestine and other organs, when introduced intravenously, and clinical results suggest that oligomers can enter human tumors upon intravenous administration and produce a therapeutic effect. Thus nowhere does Agrawal teach that one of skill would not be able to use the compounds or methods of the invention in an *in vivo* environment.

Further, the Examiner has failed to support the proposition that administration of antisense to c-raf would be unpredictable based on any objective evidence. In contrast, data are provided in the specification as filed showing the selection and design of antisense oligonucleotides to selected targets and their activity *in vitro*, as well as *in vivo*. Therefore, Applicant has clearly met their burden under 112, first paragraph. Further, Applicant respectfully reminds the Examiner that the "absence of working examples should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of

experimentation". In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). (MPEP 2164.02).

However, in an earnest effort to advance the prosecution of this case, Applicant has amended the claims as discussed *supra*. The claims as amended meet the requirements of 35 U.S.C. 112, first paragraph. Withdrawal of this rejection is therefore respectfully requested.

IV. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: October 16, 2003

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

856-810-1515